FOOD AND DRUG ADMINISTRATION
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS -- HFD-550

Medical Officer Review

VIOXX
(Rofecoxib)

NDA 21-042 (capsules) and NDA 21-052 (oral solution)
S 007 (Gastrointestinal Safety)

Submission date (letter):	June 29, 2000
Submission type:	supplement NDA
End of Review date:	March 30, 2001
Reviewer:	Maria Lourdes Villalba, MD.
Drug name:	VIOXX (Rofecoxib)
Applicant:	Merck Research Laboratories
Pharmacologic category:	NSAID (COX-2 inhibitor)
Proposed indications:	Management of acute pain, dysmenorrhea and signs and symptoms of osteoarthritis.
Dosage form and route:	Oral capsule, 12.5, 25 mg and 50 mg Oral solution 12.5 mg/5ml and 25 mg/5ml
Project Manager:	Sandra Folkendt
Related Reviews:	Stats: Qian Li, Ph.D; GI safety: Lawrence Goldkind, M.D.; CV safety: Shari Targum, M.D. Original NDA 21-042 reviews. IND 46,894 (Rofecoxib). OPDRA safety reviews

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NDA # 21-042 & 21-052, s007 – VIOXX GI safety
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NDA 21-042/052, s007 - **VIOXX Gastrointestinal Safety**

Executive summary

1. Recommendations for Regulatory Action: Approvable.

In order to adequately interpret the cardiovascular and overall safety results in the VIGOR study and provide adequate labeling information, review of the complete report of study 102 (ADVANTAGE) is necessary. A review of the safety database from the ADVANTAGE trial will allow for further global safety assessment of rofecoxib at currently labeled chronic doses and in subjects requiring cardioprotective doses of aspirin.

The applicant should be informed that labeling changes cannot be made until review of safety database from the ADVANTAGE study is complete.

2. Summary of findings

2.1 Data sources:

NDA 20-042/052 supplement 007 included three new studies (088c, 085, 090), and two studies from the original NDA (study 058 and 069). Additionally, data submitted to IND # 46,894 and post-marketing data were reviewed.

Study 088c (VIGOR) was a 8,000-patient study comparing rofecoxib 50 mg daily to naproxen 500 mg BID (median exposure was 9 months). The study excluded patients who were taking or were candidates for taking low dose aspirin (ASA). Studies 085, 090 and 058 were 6-week efficacy studies of rofecoxib 12.5 and 25 mg daily that allowed concomitant use of low dose ASA. Study 069 was a pooled analysis of GI events in the entire phase II/III osteoarthritis program. Except for study 058, all studies included in study 069 also excluded the use of low dose ASA.

As part of the IND# 46,894 (rofecoxib), the applicant conducted a 12-week 5,500-patient safety study (# 102 or "ADVANTAGE"), comparing rofecoxib 25 mg daily and naproxen 500 mg BID in a population that did not exclude the use of low dose ASA. This study was completed in March 2000, however, the complete study report has not been submitted to the FDA for review. The FDA medical reviewers have requested that the complete report of study 102, be submitted for review.

2.2 Conclusions

2.2.1. GI safety

1. The sponsor demonstrated a statistically significant reduction in PUBs and complicated PUB's, associated with the use of rofecoxib compared to naproxen in this population of patients not considered by their physicians to have an indication for cardiovascular prophylaxis with low dose ASA.

The cumulative incidence of PUB's was 1.8% and 3.9% (median exposure of 9 months) for rofecoxib and naproxen, respectively. Of note, this cumulative rate is very close to the 2 – 4% rate presented in the WARNING section of the NSAID template for patients treated for one year. The cumulative incidence of ***complicated*** **PUB's was 0.5 % and 1.2 %** in the rofecoxib and naproxen groups, respectively.

The target population for anti-inflammatory drugs includes a substantial number of patients who will need low dose ASA for cardiovascular prophylaxis. Adequate data on the safety of the chronic co-use of rofecoxib and low dose ASA do not exist. Studies that allowed the concomitant use of rofecoxib and low dose ASA were of short duration and not powered to detect differences in serious GI and CV events. Therefore, the exclusion of patients using low dose ASA is a serious limitation to the generalizability of the findings of the VIGOR study.

Different NSAIDs are associated with different risk of developing serious GI events. The only non-selective NSAID comparator included in this study was naproxen. Therefore, claims of GI superiority could be only be made in comparison to naproxen, not to all NSAIDs.

2. *The post-marketing safety profile of rofecoxib is similar to other NSAIDs, including the risk of GI bleeding. From May 1999 to October 2000, the FDA post-marketing AER system received 37 unduplicated reports of death due to gastrointestinal complications associated with the use of rofecoxib. Despite a substantial risk reduction compared to naproxen in the VIGOR study, the risk of serious GI complications associated with rofecoxib is still a concern. Risk factors associated with serious GI complications are similar to those associated with conventional NSAIDs: age, prior history of ulcer disease, concomitant use of ASA, coumadin or other antiplatelet agents, and corticosteroids.*

3. Data provided by the sponsor do not support removal of the NSAID class GI WARNING section from the VIOXX label.

2.2.2. Cardiovascular safety

1. **The cumulative rate for serious CV/thrombotic events was 1.8% (n= 45) and 0.6% (n= 19)** in the rofecoxib and naproxen groups respectively over the 9-month period. The relative risk of developing serious CV/thrombotic events was more than twice in the rofecoxib group as compared to the naproxen group (RR= 2.37; 95% C.I 1.39, 4.06; p= 0.0016, based on risk per 100 patient years). The difference was mainly due to the difference in the number of myocardial infarction (MI): 20 in rofecoxib and 4 in naproxen (crude rate 0.5 % and 0.1% for rofecoxib and naproxen, respectively) (RR= 5.0; 95% C.I. 1.72, 14.3, based on risk per 100 patient years).

In view of the cardiovascular findings the sponsor conducted a subgroup analysis of patients identified as <u>potential</u> candidates for cardiovascular prophylaxis with low dose ASA by retrospective chart review in this study. This post-hoc analysis showed that the risk of developing a CV/thrombotic event was 14.3% and 2.9% per 100 patients years, for rofecoxib and naproxen, respectively) (RR= 4.89; 95% C.I. 1.41, 16.88; p= 0.012).

For those patients in whom neither prospective physician assessment nor retrospective chart review suggested need for low dose ASA use, the risk of developing a CV/thrombotic event was 1.2% and 0.6% per 100 patient years, for rofecoxib and naproxen, respectively. (RR= 1.88; 95% C.I. 1.03, 3.45; p=0.041). Twelve of the twenty MI in the rofecoxib group and all four MI in the naproxen group were in patients who were not candidates for prophylactic aspirin, based on the sponsor's post hoc chart review.

2. The sponsor has suggested a possible cardio-protective effect of naproxen as the sole explanation for the cardiovascular findings in this study. Several issues are raised by this suggestion:

    a. Inhibition of endothelial prostacyclin synthesis (a potent vasodilator and anti-platelet agent) by selective COX-2 inhibitors has been demonstrated in pre-clinical studies. The potential effect of unopposed thromboxane A2 production (due to lack of effect on platelet COX-1) has raised concern over a possible pro-thrombotic effect of selective COX-2 inhibitors.
    b. There are no placebo-controlled studies of naproxen in the prevention of cardiovascular thrombotic events.
    c. The effect size of naproxen in this study (58% decrease risk of serious CV thrombotic events as compared to rofecoxib over a 9-month period) exceeds that reported in the literature for an anti-platelet agent in a primary or secondary prevention setting (review Table 14).
    d. Other studies (085, 090 and 102) suggest a trend of excess of MI in the rofecoxib group as compared to the active comparators.

3. The sponsor recommends that patients with known cardiovascular risk should be on prophylactic low dose ASA, however, outstanding issues are:

a. Whether the addition of low dose ASA will abolish the GI advantage of rofecoxib over naproxen.
b. Whether any of the differences in cardiovascular findings seen between rofecoxib and naproxen groups will be prevented by low dose ASA
c. Whether patients at no risk of cardiovascular disease (by standard risk factors) taking rofecoxib should be on low dose ASA.

There are no adequate data available to answer these questions. The sponsor proposes that studies 085, 090 and 058 support the safety of the concomitant use of rofecoxib and ASA. Each of these three studies was designed as an efficacy trial and neither the size (less than 1000 patients on rofecoxib taking into account all three studies) nor the duration (6 weeks) was adequate to detect significant differences in serious GI or CV events. A total of 161 patients were exposed to rofecoxib and aspirin. The dose of rofecoxib used in 085 and 090 was one fourth of the dose used in the VIGOR study.

4. In addition to the CV/thrombotic events, rofecoxib had a higher incidence of discontinuations due to HTN-related events [n= 28 (0.7%)] as compared to naproxen [n= 6 (0.2%)] and a higher incidence of CHF-related events [n= 19 (0.5%)] as compared to naproxen [n= 9 (0.2%)]. More patients in the rofecoxib group required additional cardiovascular medication as compared to the naproxen group.

5. Study 102 was a 5,500-patient study that compared rofecoxib (25 mg/day) and naproxen (1000 mg/day) for 12 weeks and allowed the use of low dose ASA. This large database contains valuable information about the concomitant use of rofecoxib and low dose ASA as well as the overall safety of rofecoxib compared to naproxen at a dose labeled for chronic use.

2.2.3. Overall safety in the VIGOR study

This risk reduction in relevant GI events did not translate into an overall safety benefit of rofecoxib over naproxen. GI safety must be assessed within the overall safety profile of a drug. Evaluation of safety by routine parameters showed no advantage of rofecoxib over naproxen:

	Rofecoxib 50 mg N=4047 (%)	Naproxen 1000 mg N=4029 (%)
a. Deaths	22 (0.5)	15 (0.4)
b. Serious AEs	378 (9.3)	315 (7.8)
c. Dropouts due to AEs	643 (15.9)	635 (15.8)
d. Serious lab AEs	3 (0.1)	0 (0)
e. Dropouts due to lab AEs	22 (0.5)	12 (0.3)
f. Hospitalizations	338 (8.4)	263 (6.6)

Body systems with the highest rate of SAE's were the Cardiovascular (2.5 and 1.1% for rofecoxib and naproxen, respectively – crude rates -) and Digestive systems (1.2 and 2.4% for rofecoxib and naproxen, respectively – crude rates -).

Other than GI and CV, the safety profile of rofecoxib and naproxen showed a similar pattern and was consistent with that of the NSAID class, although the number of non-GI NSAID-related (liver, renal, HTN and edema-related) AE's were consistently higher in the rofecoxib group. Safety profiles must be carefully analyzed based on events of comparable severity and seriousness. In the VIGOR study the potential advantage of decreasing the rate of complicated PUB's was counterbalanced by the increased rate of developing serious non-GI events (particularly cardiovascular events).

It is of note that this study employed rofecoxib 50 mg/day, a dose twice the highest recommended dose for chronic use in OA. However, 50 mg/day is the dose approved for the treatment of acute pain and post-marketing data indicate that some patients take the 50 mg dose for more than a few days. Additionally, a superior organ-specific GI safety profile may be interpreted by some as enhanced overall safety, encouraging the "dose-creep" phenomenon. Therefore, the VIOXX label should reflect the overall safety data generated in this study.